REMARKS

Claims 24 and 26-39 are pending and have been rejected.

Claims 24 and 26-39 are rejected under 35 U.S.C. §103(a) as unpatentable over Liberti et al. in view of Nichtl et al. The Office cites Liberti et al. for teaching a coating process comprising coating materials, including detergents, onto colloidal magnetically responsive particles to obtain stable microagglomerates. The process cited involves forming a liquid mixture of the particles and a coating material, subdividing the particles, allowing a coating to form on the suspended particles and recovering the resuspended particles. The Office concedes that Liberti et al. fail to teach addition of a stabilizer such as inert protein or/and polyethylene glycol after loading the particles or particles consisting of gold, silver, copper, platinum or/and palladium.

The present invention does not use this process to make coated particles. An important aspect of the present invention is that the inventors realized that biomolecules form aggregates. These aggregates, if left untreated, lead to cross-linking of the colloidal particles when the particles are added to the (aggregated) biomolecule solution. This has a negative affect on the functional stability of the biomolecule/particle conjugates because: (a) the cross-linked particles act as cores for further aggregate formation of the conjugates (this leads to reduced storage stability and effectiveness of the conjugates); (b) the cross-linked particles cannot be eluted from the matrix after drying; and (c) the cross-linked particles give blanks or unspecific signals, leading to false-positive results or too-high results.

The reason that biomolecules form such aggregates is that there appear to be hydrophobic or "sticky" patches on the

biomolecules, particularly on antibodies and other proteins, which make them interact with each other. Using detergent on the biomolecules prior to coating serves to cover those hydrophobic patches on the biomolecules. It is important to use detergent at a concentration not exceeding the critical micelle concentration for two reasons. First, micelles are undesirable as such. Second, if too much detergent is used, some detergent then would cover the particles when particles are added to the biomolecule solution and thus interfere with the formation of conjugates, i.e. the interaction between the biomolecules and the colloidal particles.

The cited art does not relate to this problem, does not discuss this problem and does not even suggest this problem should be considered. Liberti et al. teach magnetic particles which form a stable suspension. These are not the kind of particles envisaged in the present application and the two particles types should not be compared. The present invention uses colloidal particles which are not agglomerated, but are colloidal to start with. Therefore, they do not need to be separated or disrupted. In contrast, the magnetic particles of Liberti et al. are present as agglomerates which first must be disrupted to form a suspension, e.g. by sonication. During this deagglomeration process, Liberti et al. add a coating material so as to make particles which remain subdivided and do not agglomerate readily again. The coating material can be a detergent such as SDS or Tween™, a protein such as BSA or Ig, or other substances such as dextran. There is nothing whatsoever in Liberti et al. that suggests adding detergent to the coating protein before adding the particles in order to stabilize the bioactivity of the resulting conjugated particles. The detergent (or other) coating of Liberti et al. is designed to stabilize the suspension by interacting with the particles. The present invention avoids interaction of detergent with the

particles as described above and as recited in the claims here. The suspension does not need to be stabilized in the present invention because the particles already are colloidal.

The patent to Nichtl et al. relates to a conventional method of making colloidal particles, but with the additional step of stabilizing the resultant conjugates with PEG-SH after they have been formed. PEG-SH is not a detergent. Detergents are characterized and defined by being hydrophobic and hydrophilic at the same time, whereas PEG-SH is only hydrophilic.

Nichtl et al. describe prior art stabilization of already-formed conjugated particles using detergents such as Tween™, but do not describe, suggest, or even hint that detergent should be added to the material to be coated before the conjugate with the particle is formed. Stabilizers are added only after coating has already occurred in these teachings. Moreover, the method of Nichtl et al. only works because the PEG-SH is added after conjugate formation. When PEG-SH is added to the colloidal particles before (or during) interaction with the biomolecule, the SH portion of the "stabilizer" forms such a strong interaction with the particles that they are not able to bind the biomolecule. See Example 3 of Nichtl et al., which shows that "[w]hen the gold sol was pre-saturated...by adding 10^{-5}M PEG-SH...or PEG before adding a monoclonal anti-human serum albumin mouse IgG antibody..., it was found that PEG can be displaced by the antibody from the gold sol but not PEG-SH." Likewise, if PEG-SH were added to the biomolecule solution before adding the particles, it would prevent the binding of the particles to the biomolecules.

Therefore, the teachings of Nichtl et al. do not inform readers of Liberti et al. regarding methods to achieve the present invention. The two particles of Liberti et al. and Nichtl et al. are not compatible and would not be combined by the skilled person. However, even if they were combined, the most that could be

achieved using these two methods together would be a metal colloidal particle that was coated with a biomolecule and then later stabilized with PEG-SH. This would not achieve the present invention. There is no suggestion in the art, or even a hint that these teachings should be modified to add the PEG-SH or any other stabilizer to the biomolecules before coating. If such a modification were attempted using the methods of Nichtl, the resulting particles would be non-functioning.

Therefore, in summary neither Liberti et al. nor Nichtl et al., nor both references in combination teach pre-treatment of biomolecules with an amount of detergent that does not exceed a critical micelle concentration before adding the colloidal particles, and there is nothing to suggest to the skilled person that such pre-treatment might be necessary or advantageous. Applicants submit that the Office cannot meet the standards set forth in the M.P.E.P. §2143 to make out a case of prima facie obviousness and request that the rejection of these claims be withdrawn.

For the above reasons, Applicants request favorable consideration of this application.

<table>
<tr><td colspan="6">RESPECTFULLY SUBMITTED,</td></tr>
<tr><td>NAME AND REG. NUMBER</td><td colspan="5">Martha Cassidy, Registration No.: 44,066</td></tr>
<tr><td>SIGNATURE</td><td colspan="2"></td><td>DATE</td><td colspan="2">10/2/03</td></tr>
<tr><td>ADDRESS</td><td colspan="5">Rothwell, Figg, Ernst & Manbeck
Suite 800, 1425 K Street, N.W.</td></tr>
<tr><td>CITY</td><td>Washington</td><td>STATE</td><td>D.C.</td><td>ZIP CODE</td><td>20005</td></tr>
<tr><td>COUNTRY</td><td>U.S.A.</td><td>TELEPHONE</td><td>202-783-6040</td><td>FAX</td><td>202-783-6031</td></tr>
</table>